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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/825,872	04/05/2001	Alan Solomon	044137-5029-US	3133

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EXAMINER	
KAM, CHIH MIN	
ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 10/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

This is the 2nd restart being mailed out to applicant (office action dated 10/01/03 restarted). The first restart dated 07/30/04 the wrong office action was sent to applicant (office action dated 01/14/03).

Office Action Summary	Application No.	Applicant(s)	
	09/825,872	SOLOMON ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 32-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 32-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

Status of the Claims

1. Claims 1-3 and 32-57 are pending.

Applicants' amendment filed July 14, 2003 (Paper No. 13) is acknowledged. Applicants' response has been fully considered. Claims 1, 50 and 57 have been amended. Therefore, claims 1-3 and 32-57 are examined.

Rejection Withdrawn

Claim Rejections - 35 USC § 112

2. The previous rejection of claims 1, 2, 32-45, 50-52, 56 and 57 under 35 U.S.C. 112, second paragraph, regarding antecedent basis, is withdrawn in view of applicants' amendment to the claim, and applicants' response at page 4 in Paper No. 13.

Claim Rejections - 35 USC § 102

3. The previous rejection of claims 1, 3, 32-40, 46, 56 and 57 under 35 U.S.C. 102(b) as being anticipated by Kline *et al.* (WO 95/31996) is withdrawn in view of applicants' response at page 5 in Paper No. 13.

4. The previous rejection of claims 53 and 54 under 35 U.S.C. 102(b) as being anticipated by Ostberg *et al.* (U. S. Patent 5,750,106) is withdrawn in view of applicants' response at pages 5-6 in Paper No. 13.

5. The previous rejection of claims 1, 3, 32-49, 56 and 57 are rejected under 35 U.S.C. 102(a) as being anticipated by Schenk *et al.* (WO 99/27944) is withdrawn in view of

applicants' response at page 6 in Paper No. 13.

Claim Rejections - 35 USC § 103

6. The previous rejection of claims 53-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ostberg *et al.* (U. S. Patent 5,750,106) taken with Theofan *et al.* (U. S. Patent 5,643,570) is withdrawn in view of applicants' response at pages 6-7 in Paper No. 13.

Sequence Listing

7. Fig. 3 contains an amino acid sequence of the first 58 residues of mouse AA amyloid, however, sequence listing containing this sequence is not provided. Applicants must comply with the requirements of the sequence rules (37 CFR 1.821-1.825) and submit a computer readable form (CRF) and a paper copy of sequence listing, and a statement that the content of the paper and CRF are the same.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-3 and 32-57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of removing amyloid deposits from mice, comprising administering synthetic fibrils composed of immunoglobulin light chain variable-region domains to generate an immune response and to reduce amyloid deposits; or, a pharmaceutical composition comprising the synthetic fibrils, does not reasonably provide enablement for a method of removing amyloid deposits from a subject, comprising administering amyloid fibrils to generate an immune response, wherein the immune response promotes the

removal of amyloid deposits, or a pharmaceutical composition or a vaccine comprising the amyloid fibrils, where the protein in the amyloid fibrils and the subject are not defined. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 1-3 and 32-57 are directed to a method of removing amyloid deposits from a subject, comprising administering amyloid fibrils to generate an immune response, wherein the immune response promotes the removal of amyloid deposits (claims 1, 2, 32-45, 50-52, 56 and 57); or a pharmaceutical composition or a vaccine comprising the amyloid fibrils (claims 3, 46-49 and 53-55). The specification, however, only discloses cursory conclusions without data supporting the findings, which states that the present invention provides a method of removing amyloid deposits from a patient, comprising administering amyloid fibrils to generate an immune response that will promote the removal of in vivo amyloid fibrils (page 10, paragraph 0035). There are no indicia that the present application enables the full scope in view of a method of removing amyloid deposits by administering amyloid fibrils as discussed in the stated rejection. The present application provides no indicia and no teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breath of the claims, the absence of working examples, the state of the prior art and relative skill of those in the art, the unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breath of the claims:

The breath of the claims is broad and encompasses unspecified variants regarding various amyloid fibrils and the subject, which are not adequately described or demonstrated in the specification.

(2). The absence or presence of working examples:

There are no other working examples indicating a method of removing amyloid deposits from a subject by administering various amyloid fibrils except for using synthetic fibrils of immunoglobulin light chain variable-region domains to generate the immune response and to reduce amyloid deposits in mice (paragraphs 0128-0131).

(3). The state of the prior art and relative skill of those in the art:

The prior art indicates a method of treating patients suffering from amyloidogenic disease by administering amyloid-β peptide or its variants to induce immune response against amyloid deposits in the patient (Kline *et al.*, WO 95/31996; Schenk *et al.*, WO 99/27944), however, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on identities of the proteins or variants thereof in the amyloid fibrils, the treating conditions to a subject, and the effects of amyloid fibrils to be considered enabling.

(4). Predictability or unpredictability of the art:

The claims encompass a method of removing amyloid deposits from a subject, comprising administering amyloid fibrils to generate an immune response, which promotes the removal of amyloid deposits. However, the specification does not demonstrate the effects of amyloid fibrils containing various proteins or the variants thereof except for administering

synthetic fibrils of immunoglobulin light chain variable-region domains to mice. Therefore, the invention is highly unpredictable regarding the outcome of the claimed method.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a method of removing amyloid deposits from a subject, comprising administering amyloid fibrils to generate an immune response, and a pharmaceutical composition or a vaccine comprising the amyloid fibrils. The specification indicates amyloid fibril encompasses fibrils of immunoglobulin light chain, amyloid A protein, beta 2-microglobulin, transthyretin, cystatin C variant, gelsolin, procalcitonin, PrP protein, amyloid beta-protein, ApoA, lysozyme, variants thereof or allelic variants thereof (paragraph 0078). However, the specification has not identified any variant of amyloid protein in the amyloid fibrils, nor has demonstrated the administration of any amyloid fibrils containing various amyloid proteins to a subject except for administering synthetic fibrils of immunoglobulin light chain variable-region domains to mice, where the effect is disappearance of the lump (paragraphs 0128-0131). There are no working examples demonstrating the effects of amyloid fibrils containing various amyloid proteins or variants thereof in subjects other than mice. Since the specification fails to provide sufficient teaching on the identities of protein variants in the amyloid fibrils, the treating conditions such as the dose and the effects of various amyloid fibrils in the subject, it is necessary to carry out further experimentation to assess the effects of these amyloid fibrils in a subject.

(6). Nature of the Invention

The scope of the claims encompasses a method of removing amyloid deposits in a subject using amyloid fibrils to generate an immune response and to remove the in vivo amyloid deposits, and a pharmaceutical composition or a vaccine comprising amyloid fibrils, but the specification has not demonstrated the effects of various amyloid fibrils in a subject other than using a specific immunoglobulin light chain. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broad, the working example does not demonstrate the variants in the method, the outcome is unpredictable regarding the effects of various amyloid fibrils, and the teachings in the specification are limited, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the effects of amyloid fibrils containing various amyloid proteins or variants thereof in the claimed method.

In response, applicants indicate the specification (Example D) discloses mice, which are not TRIAD mice, immunized with synthetic fibrils of a immunoglobulin light chain variable-region domains and having anti-fibril antibodies, were administered a subcutaneous bolus of human AL amyloid extract to yield AL amyloidma, where the lump disappeared within 5 days indicating removal of in vivo amyloid deposits from mice; Hrncic et al. (October 2000, reference provided by applicant) indicate the monoclonal antibody (mAb) 11-1F4, generated by using heat-denatured κ4 immunoglobulin light chain protein as immunogen expedited the resolution of light-chain associated amyloid deposits in mice; Wall et al. (2001, reference provided by applicant) indicate the mAb 11-1F4 expedited the removal of systemic AA amyloid deposits, composed of serum amyloid protein A, in a murine model of inflammation-associated amyloidosis; and O'Nuallain et al. (2002, reference provided by applicant) indicate two

conformation-specific mABs WO1 and WO2, generated from fibrillar from Ab(1-40), recognize a generic amyloid fibril epitope, thus, these publications provide evidence that a fibril-specific epitope exists, which is related to three dimensional structure of the fibril, and can be used to generate 'anti-fibril" antibodies that do not react with non-polymerized precursor protein and can bind to fibrils composed of structurally unrelated precursor proteins (pages 3-4 of the response). The response has been considered, and the argument is not fully persuasive because the references (published after the priority date of the instant application, April 5, 2000) do not teach administering to a subject "amyloid fibrils" to remove amyloid deposits, they only teach anti-fibril antibody recognizes a generic amyloid fibril epitope and the administration of "anti-fibril antibody" to animal model reduces the content of amyloid, and the specification of the instant application has not demonstrated administering to a subject various amyloid fibrils containing different amyloid proteins generates immune response which promotes the removal of amyloid deposits, as encompassed by the claims, it only demonstrates the effect of a specific synthetic fibril of immunoglobulin light chain variable-region domains in mice as indicated in the section above. Thus, it requires to have additional guidance and to carry out further experimentation to assess the effects of amyloid fibrils containing various amyloid proteins or variants thereof in the claimed method.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 37, 38 and 41-45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claims 37 and 38 are indefinite because of the use of the term "cystatin C variant" or "the one or more proteins is a variant or allelic variant thereof". The term "cystatin C variant" renders the claim indefinite, it is not clear what amino acid sequence is intended as to the cystatin C variant or the variant or allelic variant of the protein, how different the variant or allelic variant is from the parent compound, and whether the variant is functional. Claim 38 is also indefinite as to "Prp protein" and "ApoA 1", it is not clear what the term means. A fully spelled out word should be indicated.

In response, applicants indicate it is well known the cystatin variant associated with amylodosis causes Hereditary cystatin Amyloid Angiopathy, which is caused by a mutation in the gene encoding the cystatin C, and the reference of Grubb et al. shows the term "cystatin C variant" refers to the Leu68Gln variant form of cystatin C. The response has been fully considered, however, the argument is not found persuasive because the specification does not identify the variant, and the claim does not recite the limitation indicated by the reference, thus it is not known which cystatin C variant is intended.

11. Claims 41-45 recite the limitation "the amyloid fibrils are removed" and "treatment of amyloid fibrils" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim, claim 1 recites "amyloid deposits".

Conclusion

12. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. CMK
Patent Examiner

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September 25, 2003

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